

REMARKS

Upon entry of the present amendment, claims 1-64 are pending in the above-referenced patent application and are currently under examination. Claims 1, 9, 45 and 51 have been amended. Claims 11, 13-44, 49 and 54-62 have been withdrawn. New claims 63 and 64 have been added. Reconsideration of the application is respectfully requested.

Claims 1 and 45 have been amended to recite that the lyophilized beads of the present invention are “substantially spherical.” Support for these amendments can be found, for example, in the specification at paragraphs [0018] and [0035].

Claims 9 and 51 have been amended to provide the full name for the acronym HEPES. This amendment finds support in the specification at page 9, line 8, for example.

New claims 63 and 64 recite the scope of original claims 1 and 45, respectively.

Applicants believe no new matter has been added by the amendments to the claims or by the new claims.

The claims are rejected in various combinations under 35 U.S.C. § 103(a). Each of these rejections is addressed below in the order set forth by the Examiner.

I. THE JONES DECLARATION

The Examiner considered the declaration by Martin Jones (“the Jones declaration”) under 37 CFR 1.132 filed on July 12, 2007 to be insufficient to overcome the obviousness rejections because the unexpected results related to features of the beads (“shape, morphology, etc.”) that were not recited in the pending claims.

Applicants respectfully note that the claims have been amended to recite that the lyophilized beads are “substantially spherical” to address the Examiner’s comments. Accordingly, the Applicants respectfully request that the Examiner reconsider the Jones declaration in view of the amended claims.

II. THE LYOPHILIZED BEADS OF THE PRESENT INVENTION ARE NOT THE RESULT OF ROUTINE OPTIMIZATION

As the Examiner states, consensus was reached during the interview of June 4, 2007 that Treml does not disclose compositions with mannitol concentrations in the range between about 53% and about 75% (w/w). Applicants note that it was also shown during the interview that the Treml compositions comprise a high molecular weight carbohydrate polymer and a second carbohydrate, where the second carbohydrate can be at most 40% (w/w) of the composition. It was also shown during the interview that the Treml reference *does not disclose mannitol*. Treml discloses many carbohydrates as useful for the second carbohydrate, including di-, tri- and polysaccharides (see col. 5, lines 29-34). However, despite this laundry list of saccharides useful for the second carbohydrate of Treml, mannitol is not disclosed. In fact, at no time during the prosecution of the instant application has the Examiner pointed to a single teaching or disclosure of mannitol in Treml.

Treml fails to disclose mannitol. Instead, Treml discloses compositions with a maximum of 40% (w/w) using a non-mannitol carbohydrate for the second carbohydrate. In doing so, Treml teaches away from the mannitol bead compositions of the present invention. Furthermore, the Jones declaration describes unexpected results sufficient to overcome the present obviousness rejections.

III. FIRST REJECTION UNDER 35 U.S.C. § 103(a) OVER PARK AND TREML

Claims 1-8, 10, 12, 45-48, 50 and 52-53 have been rejected under 35 USC § 103(a) as allegedly being obvious over Park and Treml. Applicants respectfully traverse the rejection in view of the comments below.

A claim is considered obvious “if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains” (35 USC § 103(a)). The Supreme Court in *KSR International Co. v. Teleflex Inc.*, 550 U.S. ___, ___, 82 USPQ2d 1385, 1395-97 (2007) explained what is necessary to support a conclusion of obviousness under its earlier precedent in *Graham v Deere*.

The key to supporting any rejection under 35 U.S.C. 103 is the clear articulation of the reason(s) why the claimed invention would have been obvious. The Supreme Court in *KSR* noted that the analysis supporting a rejection under 35 U.S.C. 103 should be made explicit. According to the Court in *KSR*, a finding of obviousness is supported when a prior art reference (or combination of references) (1) teaches or suggests the claim elements; (2) provides some suggestion or motivation to combine the references; and (3) provides a reasonable expectation of success (MPEP § 2143). As discussed in detail below, the cited references, whether taken alone or together, fail to satisfy all three of these requirements.

Applicants note that the claims of the present application have been amended to recite that the lyophilized beads of the present invention are “substantially spherical.”

Applicants respectfully submit that the claims of the instant invention are not obvious under 35 U.S.C. § 103(a) over Park and Treml. Park discloses a lyophilized bead for PCR where the bead can include a DNA polymerase and a stabilizer. Park discloses many polyols useful as the stabilizer, including mannitol, where the stabilizer is present in amount of about 4% by weight (see col. 4, line 24). Park, however, does not disclose a lyophilized bead being substantially spherical in shape and having mannitol in an amount between about 53% and about 75% (w/w). Accordingly, Park fails to teach or disclose all the elements of the instantly amended claims.

Nor are the deficiencies of Park remedied by Treml. First, Treml does not disclose mannitol. Second, Treml teaches away from the present invention by disclosing compositions having at most 40% (w/w) of a carbohydrate (without mentioning mannitol at all).

Moreover, the Jones declaration describes unexpected and surprising results for the lyophilized mannitol beads of the present invention.

1. Substantially spherical beads are unexpectedly prepared using mannitol of between about 53% and about 75% (w/w)

Dr. Jones declares in paragraph 5 of the Jones declaration that the instantly claimed range of mannitol of between about 53% and about 75% (w/w) is a critical range for the lyophilized beads of the present invention. Within this range, the beads are reproducibly spherical (see pictures in paragraph 5 of the Jones declaration). The substantially spherical nature of the beads is inherent to the use of mannitol in the claimed range. Outside of this range,

the beads can be non-spherical, and are characterized by a rough surface having pits and protrusions.

2. Mannitol beads unexpectedly afford substantially spherical beads as compared to beads of other saccharides

In paragraph 6 of the Jones declaration, Dr. Jones declares that the use of mannitol in the claimed range, rather than other saccharides or oligosaccharides, provides lyophilized beads that are reproducibly spherical. The pictures in paragraph 6 of the Jones declaration show the effect on bead morphology of using trehalose versus using mannitol. The beads made using mannitol are substantially spherical (E and F). In contrast, the beads made using trehalose (A and B) form a shiny, clear, irregular shaped mass that adheres to the bottom of the container, even where the % (w/v) of trehalose matches that of mannitol (A versus E). The beads made from trehalose did not lyophilize, and any resemblance to spherical shape by the trehalose beads prior to lyophilization was subsequently lost upon lyophilization.

3. The present invention unexpectedly provides lyophilized mannitol beads that are substantially crystalline

Dr. Jones declares in paragraph 7 of the Jones declaration that lyophilized mannitol beads of the present invention, surprisingly, are substantially *crystalline* rather than glassy and amorphous. Dr. Jones further declares that lyophilized beads using compositions of the prior art are glassy and amorphous, and are thus unable to make the beads of the present invention that are reproducibly spherical. The powder x-ray diffractogram for the glassy, amorphous structure demonstrated an amorphous halo with no evidence of crystallinity. The powder x-ray diffractograms for the lyophilized beads of the invention were consistent with the δ -polymorph of crystalline mannitol. Accordingly, the lyophilized mannitol beads of the present invention demonstrate a high degree of crystallinity.

4. The use of mannitol in the claimed range unexpectedly provides lyophilized beads that are reproducibly the same size

In paragraph 8 of the Jones declaration, Dr. Jones declares that the surprising nature of the lyophilized beads of the present invention is also exemplified by the reproducibility and homogeneity of the size of the lyophilized beads. Using three beads from each excipient

formulation of Table 1 in the instant application, bead cross-section was measured. The bead diameter data demonstrate that the lyophilized mannitol beads of the present invention have a high degree of uniformity, as determined by the standard deviation (SD) and the coefficient of variation (%CV). The prior art trehalose beads have a %CV of around 6.5%, while the lyophilized mannitol beads of the present invention have a %CV of from 0.70 to 2.44, significantly lower than that for the trehalose beads. The higher CV numbers for the trehalose beads indicate a larger degree of variability and less reproducibility in the diameter of the trehalose beads, as compared to the mannitol beads of the present invention. Accordingly, the lyophilized mannitol beads of the present invention are surprisingly uniform, as compared to beads with a similar % w/v trehalose.

For at least the foregoing reasons, withdrawal of the rejection is respectfully requested.

IV. SECOND REJECTION UNDER 35 U.S.C. § 103(a) OVER PARK, TREML AND KELLOGG

Claims 8 and 50 have been rejected under 35 USC § 103(a) as allegedly being obvious over Park, Treml and Kellogg. Applicants respectfully traverse the rejection in view of the comments above, as the deficiencies of Park and Treml are not remedied by Kellogg.

Kellogg discloses an antibody that inactivates a polymerase. However, Kellogg does not disclose a lyophilized bead being substantially spherical in shape and having mannitol in an amount between about 53% and about 75% (w/w). Accordingly, withdrawal of the rejection is respectfully requested.

V. THIRD REJECTION UNDER 35 U.S.C. § 103(a) OVER PARK, TREML AND SHIVELY

Claims 9 and 51 have been rejected under 35 USC § 103(a) as allegedly being obvious over Park, Treml and Shively. Applicants respectfully traverse the rejection in view of the comments below. Applicants respectfully traverse the rejection in view of the comments above, as the deficiencies of Park and Treml are not remedied by Shively.

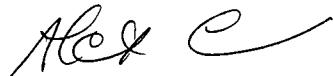
Shively discloses use of HEPES buffer in amplification reactions for Real-Time PCR. However, Shively does not disclose a lyophilized bead being substantially spherical in shape and having mannitol in an amount between about 53% and about 75% (w/w). Accordingly, withdrawal of the rejection is respectfully requested.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,



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